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CERTIFICATE OF MAILING BY FIRST CLASS MAIL (37 CFR 1.8) Applicant(s): J. Degelaen, J-M. Frere, B. Granier and B. Joris	Docket No. Neogen 4.1-48
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Application No. 10/702,507	Filing Date November 7, 2003	Examiner Bao-Thuy L. Nguyen	Customer No. 21036	Group Art Unit 1641
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Invention: **ASSAY DEVICE FOR DETERMINING ANALYTES IN A LIQUID DAIRY PRODUCT**

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September 13, 2007
Supplemental Appeal Brief

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS**

Appl. No. : 10/702,507 Confirmation No. 8535
Applicants : Jacques Degelaen, Jean-Marie Frere,
Benoit Granier and Bernard Joris
Filed : November 7, 2003
Title: : ASSAY DEVICE FOR DETERMINING ANALYTES IN A
LIQUID DAIRY PRODUCT
TC/A.U. : 1641
Examiner : Bao-Thuy L. Nguyen
Docket No. : Neogen 4.1-48
Customer No. : 21036

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Alexandria, VA 22313-1450

SUPPLEMENTAL APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Sir:

In response to the Notification of Non-Compliant Appeal Brief mailed September 4, 2007, enclosed is a Supplemental Appeal Brief which replaces the earlier Appeal Brief and which was objected to on formal grounds. The required corrections have been made.

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This is an Appeal from a final rejection in the above entitled application. The claims on Appeal are set forth in the Claims Appendix. An oral hearing will be requested. Enclosed is the fee due upon filing of the Brief.

(1) **Real Party in Interest**

The real party in interest is Neogen Corporation, Lansing, Michigan.

(2) **Related Appeals and Interferences**

There are no related Appeals or Interferences.

(3) **Status of Claims**

Claims 1-23 were cancelled in the prosecution. Claims 24, 26-32 and 34-40 are pending and on appeal. Claims 25 and 33 were cancelled and incorporated into Claim 24. No claims are allowed.

(4) **Status of Amendments**

An Amendment was filed under 37 CFR 1.116(b)(3) which was not entered.

(5) **Summary of Claimed Subject Matter**

The claims on appeal define a lateral flow type assay which is set forth in Claim 24 with the reference numbers from the drawings as follows:

24. An assay kit for detecting one or more antibiotics containing a β -lactam ring in a liquid dairy product, said assay kit comprising:

(a) an assay device comprising a solid support (1), said solid support comprising (a) a first and a second end, and (b) the following membranes (i)-(iii), fixed in succession starting from the first end,

(i) a purification membrane (2) which retains interfering substance(s) and allows antibiotics and detection reagents in the liquid dairy product to migrate by tangential capillary migration from the first end towards the second end of the solid support (1), while preserving the activity of the antibiotics and detection reagents during said migration, said interfering substance(s) being substances which prevent such migration, said purification membrane being made from non-woven polyester fibers which is capable of retaining leukocytes in the milk,

(ii) an immobilization membrane (3) comprising first and second capture substances, said first capture substance being one or more antibiotics containing a β -lactam ring which specifically bind to a receptor, which is a BlaR or BlaR-CTD protein obtained from *Bacillus*

lichenformis, said second capture substance being a substance which binds to an independent reference substance, and

(iii) an absorbent membrane (4),

(b) a detection reagent in the test kit comprising the receptor which is the BlaR or BlaR-CTD protein obtained from *Bacillus lichenformis* which specifically binds to antibiotics containing a β -lactam ring in the dairy product, and

(c) the independent reference substance.

The lateral flow assay with the BlaR and BlaR-CTD proteins is specifically set forth in the specification at pages 12 to 13, Example 1 and Figures 1 to 3.

Page 5, line 4 to page 6, line 10, details the lateral flow assay. This description is as follows:

The present invention therefore provides an assay device which allows the presence of analytes to be detected in a liquid dairy product by tangential capillary migration of the said dairy product. The assay device according to the invention comprises a solid support (1) which has a first and a second end and on which the following membranes are fixed in succession starting from the first end:

- a membrane (2) allowing the analysed liquid to be purified,
- a membrane (3) on which one or more capture substances are immobilized, and
- an absorbent membrane (4),

characterized in that the membrane (2) is capable of retaining the substances present in the dairy product which prevent the analytes, which may be present in the dairy product and the detection reagents used in accordance with the practised method, from migrating over the assay device during the tangential capillary migration of the sample after the first end of the assay device has been soaked in the analysed dairy product.

According to a particular embodiment of the invention, the assay device according to the present invention additionally possesses a membrane (5) on which at least one detection reagent has been deposited, this detection reagent being capable of solubilizing rapidly in the presence of the said dairy product. According to this particular embodiment, the membrane (5) must be placed before the membrane (3). It can be placed for example, alternatively in front of the membrane (2) at the first end of the device, or between the membrane (2) and the membrane (3), or else above or below the membrane (2).

The different membranes present in the assay device according to the present invention are superimposed on one another at their ends so as to ensure the continuous migration of the dairy product from one zone to the other. Preferably, the membrane (3) is located such that its

proximal end is located below the membrane (2) and its distal end below the membrane (4). The membranes can optionally be held in contact with one another by virtue of an adhesive plastic film (6). In this case, the adhesive plastic film is selected so as not to affect the migration of the liquid over the assay device.

The option of covering the assay device with an adhesive plastic film has two advantages: it ensures perfect contact at the point of superimposition of the membranes, and constitutes a protective film. The adhesive plastic film (6) can either cover the membranes (2), (3), (4) and (5) completely or partially cover the individual membranes. Preferably, the adhesive plastic film (6) does not cover the first few millimeters of the first end, in order to allow more rapid migration of the liquid over the membrane (2) of the assay device.

Figures 1 to 3 illustrate examples of assay devices according to the present invention. Figures 1a, 2 and 3 show front views, and Figure 1b shows a view in longitudinal section.

The solid support (1) present in the assay device according to the present invention is made of glass or plastic, preferably plastic. In the case of a support made of plastic its thickness is generally between 0.05 and 1 mm, preferably between 0.1 and 0.6 mm. The membranes are fixed on the solid support (1) by means of an adhesive.

At page 10, lines 26 to 31, the "reference reagent" is discussed as follows:

"According to one particular embodiment of the invention a third type of detection reagent is used, referred to hereinafter as "reference". This is a substance added in a known quantity to the sample analysed, which fixes itself to a specific capture substance immobilized on the membrane (3). The reference gives a band whose intensity serves as a reference for quantifying the analyte".

(6) Grounds of Rejection to be Reviewed on Appeal

(a) Claims 24, 26-32 and 36-40 were rejected as being unpatentable over Markovsky et al. (U.S. Patent No. 6,319,466) in view of Joris et al. (FEMS Microbiology Letters. Vol. 70. No. 1, 15 June 1990, pages 107-113) and Litman et al. (EP 0093613).

(b) Claims 34-35 were rejected under 35 USC 103(a) as being unpatentable over Markovsky et al. in view of Joris et al. and Litman as applied to Claim 24, and further in view of Pall et al. (U.S. Patent No. 6,074,869).

(7) Argument

(a) Claims 24, 26-32 and 36-40 were rejected under 35 USC 103(a) as being unpatentable over Markovsky et al. (U.S. Patent No. 6,319,466) in view of Joris et al. (FEMS Microbiology Letter. Vol. 70. No. 1. 15 June 1990. Pages 107-113) and Litman et al. (EP 0093613). Markovsky et al.

describes a type of lateral flow assay as illustrated in Figures 1 to 14 and described in detail in the specification. The presently claimed invention is also a type of lateral flow assay. The binding protein for the antibiotics is described in Markovsky et al. at Column 12, line 34 to Column 13, line 22 as "a beta-lactam receptor from BST (*Bacillus stearothermophilus*) is bound to a colloidal gold solution to make a beta-lactam binding protein/gold bead probe." This binding protein was well known as a receptor and was described in U.S. Patent No. 4,239,852 cited in the specification. There is no other description of any other specific bacterial protein being useful for this purpose. Thus, there is no description of a binding protein from *Bacillus licheniformis* in a lateral flow type assay as set forth in Claim 24 and the dependent claims, specifically claimed as the BlaR or BlaR-CTD protein (independent Claim 24, Claims Appendix).

Joris et al. describes BLAR proteins of about 26000 Mr which bind β -lactam antibiotics. There is no discussion of any assay, much less the lateral flow assay kit, of Claims 24, 26-32 and 36-40. There would be no way of determining from the references in combination that the

claimed test kit for dairy products with the specific receptors claimed in a lateral flow assay would be effective in determining β -lactam antibiotics in the claimed assays as set forth clearly in the Examples in the specification. It would not be obvious that these proteins would even be able to flow in an assay.

Litman et al. discloses the use of a calibration surface binding to a reagent independent from the analyte. The use of such a calibration is known but not in the claimed assay.

The prior art rejection is based upon the premise that it would be "obvious to try" to adapt the BlaR or BlaR-CTD proteins of Joris et al. to the lateral flow type of assay of Markovsky et al., even though Joris et al. does not suggest any assays at all. This type of rejection has been discussed in *KSR International Co. v. Teleflex Inc.* 82 USPQ2d, Vol. 82, No. 6, pages 1385-1400, decided April 30, 2007 and in *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), and rejected. In a complex lateral flow assay as claimed, there would be no assurance that the BlaR or BlaR-CTD proteins would function in such an assay, since the complex with the antibiotic is subjected to lateral flow.

Different proteins have very different flow characteristics as is well known in the art. One skilled in the art could not predict that the BlaR or BlaR-CTD proteins could function in this manner. Reversal of this rejection is requested.

(b) Claims 34 and 35 were rejected under 35 USC 103(a) as being unpatentable over Markovsky et al. in view of Joris et al. and Litman et al. as applied to Claim 24, and further in view of Pall et al. (U.S. Patent No. 6,074,869).

Markovsky et al. specifically discloses using support 33 as a "secondary filter" underneath the expandable sponge 32 to remove "somatic cells" in the sample assay mobile-phase support zone at Column 9, lines 7 to 14 as noted in the Office Action. There is no discussion of the use of the use of receptor BlaR or BlaR-CTD proteins for binding antibiotics. Joris et al. does not describe a lateral flow assay or any other assay. Litman et al. has been discussed. Column 6, lines 32 to 52 of Pall et al. describe types of leukocytes as blood components filtered by a melt-blown fibrous web. There is no suggestion that BlaR or BlaR-CTD bound with the antibiotics would pass through

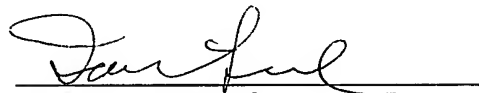
the web as described by Pall et al. One skilled in the art would have no basis for suggesting that the Pall et al. fibrous web could be used in the claimed lateral flow assay kit for dairy products as a purification membrane 2 with BlaR or BlaR-CTD antibiotic binding proteins bound to the antibiotic which have to pass through the membrane as well. Claims 34 and 35 call for a 8 μ m pore size which is small. It would not be obvious to use the claimed proteins with the BlaR or BlaR-CTD proteins for this reason. Thus, the combination of references does not suggest the claimed invention to one skilled in the art. Reversal of this rejection is requested.

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Conclusion

It is believed that Claims 24, 26-32 and 34-40 are unobvious to one skilled in the art in view of the cited art, and thus are patentable. Reversal of the Final Rejection is requested.

Respectfully,

A handwritten signature in black ink, appearing to read "Ian C. McLeod", is written over a horizontal line.

Ian C. McLeod
Registration No. 20,931

IAN C. McLEOD, P.C.
2190 Commons Parkway
Okemos, Michigan 48864

Telephone: (517) 347-4100
Facsimile: (517) 347-4103
Email: ianmcld@comcast.net

CLAIMS APPENDIX

24. An assay kit for detecting one or more antibiotics containing a β -lactam ring in a liquid dairy product, said assay kit comprising:

(a) an assay device comprising a solid support, said solid support comprising (a) a first and a second end, and (b) the following membranes (i)-(iii), fixed in succession starting from the first end,

(i) a purification membrane which retains interfering substance(s) and allows antibiotics and detection reagents in the liquid dairy product to migrate by tangential capillary migration from the first end towards the second end of the solid support, while preserving the activity of the antibiotics and detection reagents during said migration, said interfering substance(s) being substances which prevent such migration, said purification membrane being made from non-woven polyester fibers which is capable of retaining leukocytes in the milk,

(ii) an immobilization membrane comprising first and second capture substances, said first capture substance being one or more antibiotics containing a β -

lactam ring which specifically bind to a receptor, which is a BlaR or BlaR-CTD protein obtained from *Bacillus lichenformis*, said second capture substance being a substance which binds to an independent reference substance, and

(iv) an absorbent membrane,

(b) a detection reagent in the test kit comprising the receptor which is the BlaR or BlaR-CTD protein obtained from *Bacillus lichenformis* which specifically binds to antibiotics containing a β -lactam ring in the dairy product, and

(c) the independent reference substance.

26. The assay kit according to claim 24, wherein said solid support further comprises a deposition membrane having at least one deposited detection reagent, said deposition membrane being located at any position before said immobilization membrane.

27. The assay kit according to claim 26, wherein said deposition membrane is located at any position (a) before said purification membrane or (b) between said purification membrane and said immobilization membrane.

28. The assay kit according to claim 24, wherein said membranes on said solid support each are fully or partially covered by an adhesive plastic film.

29. The assay kit according to claim 28, wherein said adhesive plastic film does not cover the first few millimeters of said assay device.

30. The assay kit according to claim 24, wherein said detection reagent is coupled with at least one labeling agent.

31. The assay kit according to claim 30, wherein said labeling agent is fluorescent, particulate, radioactive, luminescent or enzymatic.

32. The assay kit according to claim 24, wherein the antibiotic to be detected by the test kit is selected from the group consisting of benzylpenicillin, ampicillin, amoxicillin, carbenicillin, methycillin, cloxacillin, 6-APA, monolactam, aztreonam, mecillinam, cephalixin, cephaloglycine, cephaloridine, nitrocephin, cefatoxime, defuroxime, ceftiofur, cephapirin, and 7-ACA.

34. The assay kit according to claim 24, wherein said purification membrane comprises a pore diameter of about 8 μ m.

35. The assay kit according to claim 24, wherein said purification membrane comprises a pore diameter of about 8 μ m, is capable of about 40-80% immobilization of the leukocytes, and is hydrophilic.

36. The assay kit according to claim 24, wherein the one or more antibiotics in the liquid dairy product can be detected within 5 minutes or less.

37. The assay kit according to claim 24, which can detect penicillin G at a concentration of 3 ppb.

38. The assay kit according to claim 24, which can detect ampicillin at a concentration of 4 ppb.

39. The assay kit according to claim 24, which can detect amoxycillin at a concentration of 4 ppb.

40. A method for detecting one or more antibiotics in a liquid dairy product within 5 minutes or less using the assay kit according to claim 24, which comprises:

(a) placing a determined volume of the liquid dairy product in contact with an excess amount of the detection reagent of claim 24 relative to the amount of antibiotic or antibiotics in the liquid dairy product, the detection reagent comprising the receptor which specifically binds to antibiotics containing a β -lactam ring obtained from *Bacillus lichenformis*, to form a mixture,

(b) incubating the mixture under conditions which allow for formation of a complex between the antibiotic or

antibiotics which are present in the liquid dairy product and the detection reagent,

(c) placing the mixture in contact with the first end of the solid support of the assay device of claim 24, to permit capillary migration of the mixture through the assay device, wherein said first capture substance forms a complex with the detection reagent which is not complexed with the antibiotic or antibiotics in the liquid dairy product, and

(d) detecting the antibiotic or antibiotics in the liquid dairy product by determining the amount of the detection reagent complexed with said first capture substance, wherein the amount of the detection reagent complexed with said first capture substance is inversely proportional to the amount of the antibiotic or antibiotics in the liquid dairy product.

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EVIDENCE APPENDIX

(None.)

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RELATED PROCEEDINGS APPENDIX

(None.)